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EXAMINER

STAPLES, MARK

ART UNIT

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1637

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|--|--|
| Office Action Summary | Application No. 10/547,669 | Applicant(s) CALISTRI ET AL. | |
| | Examiner MARK STAPLES | Art Unit 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01/22/2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 9, 10, and 12 is/are pending in the application.
- 4a) Of the above claim(s) 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 9 and 10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment of claims 1 and the cancellation of claims 2, 4-8, and 13-22 in the paper filed on 01/22/2009 is acknowledged. Claim 12 remains withdrawn.

Election/Restrictions

2. Newly submitted claim 1 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 1 recites non-elected species of SEQ ID NOs.: 1-8, 11, and 12.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, SEQ ID NOs.: 1-8, 11, and 12 of claim 1 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 9, and 10 consonant with original election of SEQ ID NOs: 9, 10, 13, 14, 15, and 15 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration under 37 CFR 1.132 is insufficient

3. The Declaration under 37 CFR 1.132 filed 01/22/2009 is insufficient to overcome the rejections of pending and at issue claims 1, 9, and 10 based upon Shuber (2001) under 35 U.S.C. 102(b), further in view of Zhou et al. (2002) under 35 U.S.C. 103(a), and further in view of Kmiec et al. (2001), Kmiec et al. and Albertsen et al. (2001), and Buck et al. (1999) under 35 U.S.C. 103(a) as set forth in the last Office action because: the declaration does not provide evidence that use of the claimed primers of SEQ ID NOs: 1-16 versus different and newly designed primers for determining the presence of colorectal tumors or precancerous lesions gives differences in results which are in fact unexpected and unobvious and of both statistical and practical significance. The evidence relied upon should establish “that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.” *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). See MPEP § 716.02(b) [R-2] I. Absence of property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness. *Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985). See MPEP § 716.02(a) [R-2] IV.

It is noted that the type of variability in results with different primers as given in the Declaration are expected based upon the prior art teaching of Buck et al. (entire article, especially Figure 2).

Furthermore, the Declaration does not state or indicate that differences in the results are unexpected.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Objections and Rejections that are Moot / Withdrawn

Canceled Claim Objection and Rejections Moot / Withdrawn

4. The objection and/or rejections of canceled claims 2, 4-6, 8, 11, 13-19, 21, and 22 are moot and therefore are withdrawn.

Claim Objection Withdrawn

5. The objection of claim 1 for improper grammar is withdrawn, as Applicant has deleted the phrase "with fluorescent molecule" which was improper grammar.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

6. The rejection of claims 1, 9, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Applicant has overcome this rejection by amending claim 1 to recite how the reference value is determined.

Claim Rejections Withdrawn - 35 USC § 102(b)

7. The rejection of claims 1, 9, and 10 under 35 U.S.C. 102(b) as being anticipated by Shuber (WO 2001/42502) is withdrawn. Applicant's arguments have

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been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Canceled Claim Rejections Withdrawn - 35 USC § 103(a)

8. The rejection of canceled claim 2 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) and further in view of Zhou et al. (2002) is moot and therefore is withdrawn. Applicant's arguments with respect to canceled claim 2 are moot.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 112 Second Paragraph

9. The rejection of claims 1, 9, and 10 under 35 U.S.C. 112, second paragraph is maintained. The term "pre-cancerous lesion" in claim 1 remains in the preamble of claim 1 and is a relative term which renders the claim indefinite. The term "pre-cancerous lesion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Dependent claims 9 and 10 are thus also indefinite. Applicant does not argue against this rejection. It is noted that Applicant has deleted "pre-cancerous lesions" from step e of claim 1.

New Rejections Necessitated by Amendment

New Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001, previously cited), Kmiec et al. (W0 2001/73002, previously cited), Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited).

Although this is a new rejection necessitated by amendment, it is noted that Applicant argues that the claimed invention has an unexpected sensitivity improvement

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over the cited prior art and refers to the Rule 132 Declaration. However, Examiner has not found persuasive evidence of an unexpected sensitivity improvement, as given above. Thus Applicants arguments do not overcome this rejection, as follows.

Regarding claims 1 and 9, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:
a) extracting DNA from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");

b) PCR amplifying at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labelled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA, the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2);

c) quantifying the amplified fragments (amplicons);

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d) calculating the total amount of different amplicons;

e) comparing the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as “Q#”, which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the “NEG CONTROL” as a reference value, and in Figures 1-7 is also compared to the “POSITIVE CONTROL” as another reference value). Shuber further teaches that a total amount of amplicons, that is amplifiable nucleic acid, is indicative of disease by teaching: “As shown in those figures [11A and 11B], patients with [colorectal] cancer or adenoma have an increased yield of amplifiable DNA.” (see p. 22 lines 20 and 21).

Further regarding claim 1, Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 1 of Office Action mailed on 03/28/2008).

Further regarding claim 1, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: “Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient”; and see p. 10, 2nd paragraph, 3rd sentence: “A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples”).

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Further regarding claim 1, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight, as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catenin, mlh-1 , pms-1 , pms-2, pol-delta, and bax").

Shuber does not teach other elected sequences of instant claim 1 comprising SEQ ID NOs: 10, 13, 14, 15, and 16.

Regarding claim 10, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to... machine-driven optical comparison, densitometry,... and other known means").

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 1 of Office Action mailed on 03/28/2007).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 1 of Office Action mailed on 03/28/2007).

Albertsen et al. do not teach SEQ ID NOs: 9, 10, 13, 14, or 16; or sequences comprising these.

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 1 is rejected for SEQ ID NOs: 9, 10, 13, 14, 15, and 16, as described following. With regard to Claim 1, for primers designed for amplification of APC gene, Shuber, Kmeic et al. and Albertsen et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 9, 10, 13, 14, 15, and 16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 9, 10, 13, 14, 15, and 16 are contained within the sequences disclosed by Shuber, Kmeic et al. and Albertsen et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 9, 10, 13, 14, 15, and 16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC

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gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Conclusion

13. No claim is free of the prior art.
14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples

/M. S./

Examiner, Art Unit 1637

April 9, 2009

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637